

# LEAD-POISONING IN FROGS.

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## LEAD-POISONING IN FROGS.<sup>1</sup>

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THE influence which the absorption of lead exerts upon the system of a cold-blooded animal seems to have been commonly regarded as requiring no investigation, for I have been unable to find so much as an allusion to the subject in any of the general treatises on poisons, or in any of the numerous monographs on lead-poisoning.

This appears all the more remarkable when one considers the important services which experiments upon the frog have rendered, in discovering the mode of action of other toxic substances.

Hermann, in his "Treatise on Experimental Toxicology" (Berlin, 1874), when writing (page 24) on the choice of animals for experimentation, and naming, in order, man, warm-blooded, cold-blooded, and invertebrate animals, says:

"Among these, cold-blooded animals occupy the highest rank by reason of their availableness. The same qualities which have made the frog, after a well-known expression, the martyr of physiology, make him also the martyr of toxicology. . . . While, in warm-blooded animals, all poisons which by paralyzing the heart interrupt the circulation, or which by interference with respiration alter the proportions of gases in the blood, cause intense functional disturbance in all other organs, in the frog, the toxic effects above named have no influence on the condition of other organs, like the nervous and muscular apparatus, for example. Disturbance in

<sup>1</sup> Read before the American Neurological Association, June, 1877.

the muscular and nervous systems, observed in the frog after poisoning, is surely to be ascribed to the direct effect of the poison upon these organs, and not to an indirect effect through a simultaneous disturbance of the heart, the breathing-apparatus, etc. . . . Recent toxicology has therefore been perfectly right in directing its attention to the frog."

The following experiments are a few selected from a large number which I have made during the past year. The animals were carefully examined every day, and the results, as noted, are now presented to the Association, in the hope that the subject may prove a suggestive and attractive one to other observers.

I. ACUTE POISONING.—Orfila (*Éléments de Toxicologie*, 1843, tome i., p. 633), Dr. Gaspard (*Journal de Physiologie Experimentale*, 1821, tome i., p. 284), and, more recently, Dr. René Moreau (*Recherches Cliniques et Experimentales sur l'Empoisonnement aigu par le Plomb et ses Composés*, 1875), have given us the results of intra-venous injections of the salts of lead in dogs. Little effect was produced by the subcutaneous method of injection, and this failure is ascribed by Moreau to the slowness of absorption caused by the astringent action of the lead salts.

EXPERIMENT 1. *March 9, 1876, 3 P. M.*—I inject  $1\frac{1}{2}$  grain of the acetate of lead under the skin (dorsal region) of a large frog (*Rana Temp.*). *6 P. M.*—The animal remains motionless when touched. When turned upon its back it regains the normal position without difficulty. *8 P. M.*—Voluntary or reflex movements can no longer be excited.

*March 10th, 10 A. M.*—Heart exposed, and found to be motionless, much enlarged, and filled with blood. Cardiac movements cannot be excited by pricking or by electricity. Muscles of the trunk and extremities, with their nerves, respond normally to electric irritation. This may be taken as a good example of acute poisoning by this salt.

The action of the poison in thus sparing the motor nerves of the extremities, and in being limited to the organs of respiration and circulation, will be found to correspond quite closely with the results obtained by Rouget<sup>1</sup> and those by Sklärek,<sup>2</sup>

<sup>1</sup> "Arch. de Physiologie," 1873, p. 336.

<sup>2</sup> "Arch. für Anat. u. Phys.," 1866, p. 481.

the former experimenting with the nitrate of silver, and the latter with arsenic, both employing the frog.

This experiment I have often repeated, and, although from twelve to twenty-four hours are required for the action of the poison to manifest itself, its effects are constant in this species (*Rana Temp.*).

II. CHRONIC POISONING.<sup>1</sup>—The more gradual absorption of lead through that here important organ of respiration, the skin, is followed by symptoms which differ widely from those noted above. In 1871, E. Heubel<sup>2</sup> gave, at short intervals, small doses of the acetate of lead to eight dogs, during periods varying from two to eight weeks. Wasting and paresis of the muscles of the posterior and anterior thoracic regions and of the posterior extremities resulted, but no typical lead paralysis was observed, nor were the electrical reactions given. The above are the latest, and, as far as I can ascertain, the only published experiments, made with the object of causing the symptoms of chronic lead-intoxication in animals.

EXPERIMENT 2. *March 22, 1876.*—Four small frogs (*Rana Temp.*) are placed in a glass globe containing: water, 24 fl. oz.; acetate of lead, 1 gr.

25th.—No change observable.

28th.—Frogs lively. Solution made stronger by addition of seven grains of the lead salt.

29th.—No effect observable.

*April 3d.*—One frog motionless. Posterior extremities paralyzed. Anterior extremities respond to the will. All the muscles of the posterior limbs respond far better to the action of the voltaic than to that of the faradaic current. Division of the spinal cord causes no movement in the lower limbs. Direct irritation of the sciatic nerves by electricity gives rise to no muscular contraction except in the peroneal muscle of one leg, causing slight flexion of the foot. Heart normal in size and action. The faradaic current used in these

<sup>1</sup> I use the word "chronic" on account of the longer time which elapses before the poison affects the system, and of the constancy of the paralytic symptoms.

<sup>2</sup> "Pathogenese und Symptome der chronischen Bleivergiftung. Experimentelle Untersuchungen."



tests was from the second spiral of Du Bois-Reymond's apparatus. The voltaic current was supplied by small cells containing zinc and copper in pure water.

5th.—Two more frogs motionless. Motor nerves of lower limbs have completely lost their irritability. Muscles respond but little to direct faradization, while the voltaic current made to act on the same parts causes well-marked contractions and movements of the limbs. The hearts of both are normal, and beating rhythmically.

EXPERIMENT 3. *April 5th.*—The remaining specimen, with three others of the same species, are placed in: water, 24 fl. oz.; acetate of lead, 8 grains.

6th.—Frog from experiment 2 motionless. Reaction in nerves and muscles to electrical tests is found to be the same as that observed in the foregoing cases.

7th.—Desquamation is very active. This is a constant result, and due to the action of the solution. Microscopic examination of the cast-off membranes shows them to consist solely of a pavement epithelial layer.

10th.—Since the 7th there has been little to observe. To-day all three animals are motionless. Condition of nerves and muscles, and their electrical reactions, are found to be the same as in the previous cases. Hearts of normal size, and beating.

I have frequently noticed that some of the frogs always croaked as if in pain whenever the spine was pressed gently between the thumb and forefinger. The cries were provoked with much the same regularity as those caused by stroking the back after Goltz's experiment of separating the cerebrum from the parts below.

EXPERIMENT 4. *April 25th.*—A large bull-frog (*Rana Pipiens*) is placed in a solution: water, 48 fl. oz.; acetate of lead, 16 grains.

26th.—From being very inert, the animal shows signs of hyperæsthesia. Springs violently when touched lightly with the finger.

*May 1st.*—Since the 26th, moderate pressure on one side of the abdomen with the smooth end of a glass rod has caused violent jumping and loud croaking.

2d.—No signs of hyperæsthesia. When placed on the back, regains the normal position, but quite slowly.

9th.—Quantity of lead increased to 48 grains.

12th.—Frog is motionless. It cannot turn over when placed on the back. Electrical reaction of the sciatic nerves is completely lost. That of the muscles is the same as in the preceding experiments, viz.: nearly lost to faradization, but quite marked with voltaic excitation. Heart of normal size, and beating normally. In this species of frog, probably on account of their large size and toughness of the skin, much stronger solutions of lead are often required than even with large specimens of *Rana Temporaria*. In fact, I have kept one two months in a lead solution (one grain to the ounce) without being able to note any change in his condition, excepting that of active desquamation. Some of this species certainly enjoy the same immunity from the usual action of lead when injected under the skin. I kept alive and active for thirteen days a large bull-frog, which was submitted to three subcutaneous injections of four grains each of the acetate of lead, on three successive days, beginning May 4, 1877. On May 17th the animal was found motionless. The heart was paralyzed, as in Experiment 1, and distended to twice its natural size. No contractions of this organ could be induced by the usual mode of irritation. After cutting it so as to allow the blood to escape, contractions began, nearly normal in quality. This was at 2 P. M. At 9 P. M. the muscles still retained their faculty of contracting to faradaic stimulus. At the same time (May 4th) one grain of the salt was given in the same manner to a vigorous specimen of *Rana Temporaria*, and in twenty-four hours the heart was motionless.

From these exceptional cases we have only additional proof that the power of resisting the action of this poison, which is so noticeable in the systems of painters and others, all equally subjected to the same toxic influence, exists also in individuals among the lower animals.

Analysis of a sufficient number of experiments has convinced me of the truth of the following conclusions:

I. The rapid absorption of the acetate of lead soon causes

death by stoppage of the heart's action—an effect probably common to all the mineral poisons.

II. The slow absorption of this salt through the skin induces in the voluntary muscles of the frog a paralytic state, identical in its most important features with that which one sees so frequently in man.

In the acute form the motor nerves and muscles are unaffected; in the chronic form the heart is spared.

The paralysis is developed somewhat rapidly; there is no wasting of the muscles; faradization has little or no effect in inducing muscular contractions, while the voltaic current acts well in this respect;<sup>1</sup> cutaneous sensibility is seldom entirely lost, and before the complete development of paralysis it often seems to be increased.<sup>2</sup>

Microscopic examination of the web of the foot, which was made in a large proportion of cases, showed marked spasm of the arterioles, and dilatation of the venules, with consequent slowing of the circulation. The large veins of the extremities are generally congested, and sometimes varicose. The muscles are paler, and firmer to the touch than when in the normal condition, although there is no rigidity of the limbs.

My attention has been especially directed to the elements of the spinal cord. Comparison of sections of this portion of the nervous system, taken from frogs which have succumbed to the slow action of lead, with a large number made from the normal cord, has thus far shown no difference which is constant. In some cases the blood-vessels seem much increased in number and size, and the nerve-corpuscles of the anterior

<sup>1</sup> The gastrocnemius and sartorius muscles were tested often in Pflüger's myographium. Polar action of electricity is not marked as in healthy muscles. Cathode closing is no more effective than anode closing. There are no opening contractions with mild currents. Contraction is slow, the organ remaining shortened for some little time during the passage of the current. The affected muscle never reacts so powerfully to either form of current as does a healthy one.

<sup>2</sup> Frogs placed in solutions of arsenious acid, bichloride of mercury, or nitrate of silver, die almost as rapidly as they do after subcutaneous injections of these poisons. With neither of these three salts have I been able to produce the same result as that caused by the lead-bath.



horns appear to be less numerous than in the healthy condition. Nothing like structural or pigmentary degeneration has been seen. The sympathetic system has not been examined.

It is almost certain that the poison is capable of acting primarily either upon the muscular substance or upon some portion of the nervous system. If the alterations are anatomical, they ought to be found. The spinal cord of batrachians is especially adapted to such researches, as the anterior horn-cells are very large, and in the lumbar region are closely crowded together in a definite, easily-determined space. Thus far I have not been very successful with Sokolow's<sup>1</sup> method in finding even the normal nerve-terminations in the muscles, but there is every reason to believe that others may be more fortunate.

In fresh preparations I have as yet found no alteration of the muscular or nerve fibres.

Although the existence of Erb's "entartungs-reaction" is strong evidence of a separation of the muscles from their spinal nerve-cells, conclusive proof of this is only to be found by the discovery of that portion of the nervous system where the process of separation begins. The latest authorities favor the view that this affection is of neurotic origin, and their arguments lack nothing but anatomical support. Westphal with characteristic fairness freely admits the doubtful interpretation to be placed upon the changes observed in his case of radial paralysis, and it is certainly unfortunate, from a scientific point of view, that his researches cannot be more frequently made in man.<sup>2</sup> The close resemblance, as to symptomatology, of some cases of generalized lead-paralysis with<sup>3</sup> "spinal paralysis of the adult," in which there is much reason for accepting the coexistence of myelitis of the anterior horns, goes far to encourage us in assuming that these portions of

<sup>1</sup> "Sur les transformations des terminaisons des nerfs de la grenouille après la section des nerfs." "Arch. de Physiol.," 1874, p. 300.

<sup>2</sup> C. Westphal, "Ueber eine Veränderung der Nerv. radialis bei Bleilähmung." "Arch. für Psychiatrie," etc., Bd. iv., S. 776.

<sup>3</sup> E. C. Seguin, "Myelitis of the Anterior Horns," etc. New York, 1877.

the spinal cord are first affected by the poison in the higher animals.

May not our knowledge of the pathogeny<sup>1</sup> of lead-paralysis acquire a surer basis than it now possesses by further researches on lead-poisoning in frogs?

<sup>1</sup> "Zur Pathogenese der Bleilähmungen." Von Dr. Ernst Remak. "Arch. für Psychiatrie," etc., Berlin, 1875, Bd. vi., S. 1. This instructive paper contains numerous references to the literature of the subject.